

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

BIANCHETTI BRACCO MINOJA S.R.L.
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RECEIVED ON

11 MAG. 2005

BIANCHETTI-BRACCO-MINOJA srl

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference SCB 889 PCT	Date of mailing (day/month/year) 11/05/2005
International application No. PCT/EP2004/014359	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant BIO 3 RESEARCH SRL	International filing date (day/month/year) 16/12/2004

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**


Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sylvia Hermier
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/EP2004/014359International filing date (day/month/year)
16.12.2004Priority date (day/month/year)
19.12.2003

International Patent Classification (IPC) or both national classification and IPC

A61K31/198, A61K31/225, A61K31/185, A61K31/385, A61K31/07, A61K31/375, A61K31/355, A61P13/12,

Applicant

BIO 3 RESEARCH SRL

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Cielen, E

Telephone No. +31 70 340-4540



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/014359

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/014359

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 7-9

because:

- ☒ the said international application, or the said claims Nos. 7-9, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/014359

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims 4
No: Claims 1-3,5-9

Inventive step (IS)

Yes: Claims
No: Claims 1-9

Industrial applicability (IA)

Yes: Claims 1-6
No: Claims

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

10/583334

AP3 Rec'd PCT/PTO

16 JUN 2006
International application No.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

PCT/EP2004/014359

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 7-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Present claims 7-9 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

- D1: US-A-4 794 124 (YAMAMOTO ET AL) 27 December 1988 (1988-12-27)
- D2: US-A-4 849 452 (DULCE ET AL) 18 July 1989 (1989-07-18)
- D3: WO 93/14750 A (THE ROCKEFELLER UNIVERSITY; ALTEON INC) 5 August 1993 (1993-08-05)
- (D4) US-A-5 607 974 (DROEGE ET AL) 4 March 1997 (1997-03-04)
- (D5) US-A-4 792 549 (TAKAHASHI ET AL) 20 December 1988 (1988-12-20)
- (D6) WO 02/34303 A (NITROMED, INC; TRUSTEES OF BOSTON UNIVERSITY; LOSCALZO, JOSEPH; VITA,) 2 May 2002 (2002-05-02)
- (D7) US 2002/137785 A1 (KINDNESS GEORGE ET AL) 26 September 2002 (2002-09-26)

26)

- D8: US-A-6 060 446 (ZALOGA ET AL) 9 May 2000 (2000-05-09)
- D9: DATABASE WPI 6 September 1991 (1991-09-06), Derwent Publications Ltd., London, GB; Class 914, page 2, AN 1991-306713 XP002326744 FUNATO TOSHIAKI ET AL.: "Oral amino acid preparation for cardiac failure" & JP 03 204814 A (OTSUKA SEIYAKU KOGYO KK) 6 September 1991 (1991-09-06)
- D10: DE 34 14 491 A1 (DIETL, HANS, DR) 24 October 1985 (1985-10-24)
- D11: MOBERLY JAMES B ET AL: "Elevation of whole-body glutathione in peritoneal dialysis patients by L-2-Oxothiazolidine-4-carboxylate, a cysteine prodrug (Procysteine)" JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 9, no. 6, June 1998 (1998-06), pages 1093-1099, XP008046078 ISSN: 1046-6673
- D12: US-B1-6 627 659 (SANTANGELO FRANCESCO) 30 September 2003 (2003-09-30)
- D13: WO 00/53176 A (UNI-CI S.R.L; DALL'AGLIO, ROBERTO; BORGONOVO, MARGHERITA; INTROINI, CA) 14 September 2000 (2000-09-14)
- D14: WO 00/44375 A (MARS UK LIMITED; HARPER, E., JEAN) 3 August 2000 (2000-08-03)
- D15: EP-A-0 958 816 (ASTA MEDICA AKTIENGESELLSCHAFT) 24 November 1999 (1999-11-24)
- D16: M. H. BEERS; R. BERKOW: "The Merck Manual of Diagnosis and Therapy, Seventeenth Edition" 1999, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION N.J., XP002326823

V.iii. Article 33(2) PCT.

(a) Attention is drawn to the fact that claims 4 and 7-9 relate to a dosage regimen. In the European phase, a feature in a claim which related merely to the prescription of a specific drug regimen for basically known medical treatments, cannot be considered to represent a further medical indication from which novelty can be derived on the basis of the principles set out in decision G5/83.

Moreover, determination of the best individual treatment schedule, in particular the

prescribing and modification of drug dosage regimens used for administering a particular medicament, so as to comply with the specific needs of a patient and to achieve the desired result of the treatment in an individual patient, is typical of the non-commercial and non-industrial medical activities which should remain free from restraint.

(b) The scope of claim 6 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any document disclosing a medical use of a composition suitable for oral administration comprising cysteine or cystine will be novelty-destroying for the subject-matter of those claims.

(c) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3 and 5-9 is not new in the sense of Article 33(2) PCT.

✓ 1. Document D1 discloses the use of orally administered cysteine for the treatment of diabetic complications, such as nephropathy, which falls within the definition "acute or chronic kidney diseases" (column 2, lines 25-54; column 6, lines 10-16). The daily dose ranges from 10-5000 mg, in single or divided dosages (column 3, lines 1-13). According to D16, diabetic nephropathy is a major cause of chronic renal failure and the most common cause of end-stage renal disease (Table 222-3; p. 1845, paragraph bridging left- and right-hand column); therefore, treatment of diabetic nephropathy prevents chronic kidney failure and end-stage renal disease. Therefore, the subject-matter of present claims 1, 3, 6 and 8-9 is not novel over D1.

✓ 2. Document D2 reports the use of L-cysteine in an amount of 0.75g/dose for the treatment of nephro-urological disorders, such as kidney stones (column 2, lines 24-44; column 2, line 60 - column 3, line 11; claims). Therefore, the subject-matter of present claims 1, 3, and 6 is not novel over D2.

3. Document D3 teaches the use of an agent which inhibits the formation of advanced glycosylation end products of target proteins, such as cysteine, for the treatment of diabetic kidney disease or glomerulonephritis (p. 5, line 13 - p. 6, line 6; p. 6, lines 29-32; p. 7, lines 14-20; p. 17, lines 6-22); claims 1, 7, 15, 17, 18, 31). The compositions can be administered orally (claim 14). According to D16, glomerulonephritis is a major cause of acute renal failure (Table 222-1); therefore, treatment of glomerulonephritis prevents acute kidney failure. Therefore, the subject-matter of present claims 1 and 6 is not novel over D3.

4. Document D4 discloses the treatment or prevention of diseases related to reduced intra-cellular cysteine, such as renal failure or hemodialysis, with a cysteine source, e.g. N-acetylcysteine, N-formylcysteine or cysteine (column 1, lines 51-59; column 2, lines 11-40).

The compositions can be administered orally, e.g. in the form of tablets containing from 100 mg-1g active substance (column 2, lines 53-67; column 3, lines 14-19).

According to D16, untreated chronic renal failure progresses from moderate to end-stage disease (p. 1847, left-hand column, par. 4); therefore, treatment or prevention of renal failure prevents end-stage renal disease. Therefore, the subject-matter of present claims 1-3 and 6-9 is not novel over D4.

5. Document D5 discloses the use of an amino acid composition, containing cysteine or cystine as preferred amino acids, optionally in combination with vitamins or aspartic acid, for the treatment of patients with renal diseases (column 1, lines 5-9; column 2, lines 58-67; examples 1, 2, 4-6; claims). Therefore, the subject-matter of present claims 1, 5 and 6 is not novel over D5.

6. Document D6 teaches the treatment of vascular diseases resulting from NO insufficiency, e.g. renal failure or insufficiency, or oxidative stress, such as chronic renal disease or hypertension-dependent end-stage-renal disease with a combination of a anti-oxidant, such as cysteine, and a NO-donor (p. 1, lines 9-17; p. 14, line 23 - p. 15, line 8; p.21, lines 4-13; p. 22, lines 18-22; claims 1, 3, 4, 14, 17, 23-25, 27, 44-45, 47, 49-51). Oral administration is possible (p. 30, lines 18-23). Therefore, the subject-matter of present claims 1 and 6 is not novel over D6.

7. Document D7 discloses a combination of a leukotriene antagonist and cystine or cysteine and optionally lipoic acid to combat inflammatory diseases, such as ischemic renal failure (par. [0002], [0004], [0009], [0015], [0018], [0042], [0044]-[0045]; claims 1, 29). The administration can be oral, e.g. 140 mg twice a day (par. [0034]). Therefore, the subject-matter of present claims 1, 5 and 6 is not novel over D7.

8. In document D8, the use of a nutritional composition to prevent or treat acute renal failure is disclosed (column 1, line 60 - column 2, line 2; column 2, lines 27-30; column 5, line 30 - column 6, line 59; claims 1, 2, 6). Cysteine may be used to prevent injury to the kidney (column 4, lines 31-40). Therefore, the subject-matter of present claims 1, 5 and 6 is not novel over D8.

9. Document D9 discloses an oral amino acid preparation for renal insufficiency containing cysteine or cystine. Therefore, the subject-matter of present claims 1, 5 and 6 is not novel over D9.

10. Document D10 discloses oral amino acid mixtures, which may contain cysteine or cystine, for the treatment of acute or chronic (with or without dialysis) renal insufficiency (claims 1, 3, 5, 6; p. 3, lines 1-32; p. 4, line 11 - p. 5, line 25; p. 6, lines 26-30). The

composition improves the therapy outcome for patients on dialysis. Therefore, the subject-matter of present claims 1, 2, 4 and 6 is not novel over D10.

11. Document D11 reports that oral L-2-Oxothiazolidine-4-carboxylate (OTZ), a cysteine prodrug, administered in 500 mg capsules, may limit oxidative damage to peritoneal membrane during dialysis of patients with chronic renal failure (abstract; p. 1094, left-hand column, par. 2; p. 1094, right-hand column, par. 2; p. 1097, right-hand column, par. 3 - p. 1098, left-hand column, par. 2). The compound raises cellular glutathione levels by providing a source of cellular cysteine (p. 1093, right-hand column, par. 2). D11 clearly teaches that it is the increased supply of cellular cysteine which is responsible for the raise in cellular glutathione concentration and hence an improvement in antioxidant status in dialysis patients (p. 1098, left-hand column, par. 2). Therefore, the subject-matter of present claims 1-3 and 7 is not novel over D11.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of alternative medicaments for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure or for the treatment or prevention of acute or chronic kidney diseases or end-stage renal disease. The proposed solution is the use of oral cystine and/or cysteine.

(b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-9 - as far as novel - does not involve an inventive step in the sense of Article 33(3) PCT.

Even if novelty could be restored, the present application would very likely lack inventive step over each of D1-D11, which clearly teach the use of oral cysteine or cystine for the claimed diseases.

(c) In addition, as far as the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure is concerned (claims 1-5 and 7), the subject-matter of these claims does also not involve an inventive step for the following reasons:

Document D12, which can be considered to represent the closest state of the art, discloses that intravenous administration of N-acetylcysteine decreases the effects of oxidative stress in patients with renal disease undergoing hemodialysis. A study is mentioned

wherein the oral administration of N-acetylcystein for the same purpose was ineffective.

The subject-matter of present claims 1-5 and 7 differs herefrom in that oral cysteine or cystine is used for the same therapeutic purpose.

The problem to be solved by the present application may therefore be regarded as the provision of an alternative cysteine source, offering advantages in terms of cost, ease and safety, for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure (present description, p. 5, lines 4-8).

The solution proposed in claims 1-5 and 7 of the present application cannot be considered as involving an inventive step for the following reasons:

Document D13 discloses a synergistic combination of lipoic (thioctic) acid and cysteine, cystine or N-acetylcysteine, for the treatment of conditions caused by oxidative stress (p. 1, lines 3-15; p. 1, line 26 - p. 2, line 1; p. 2, lines 22-34; claims 1, 3, 4, 7). Optionally, other anti-free radicals, such as vitamins E or C can be coadministered (p. 5, line 33 - p. 6, line 20). In a preferred embodiment, the compositions can be formulated in tablets or capsules (p. 7, lines 6-12; p. 8, lines 12-15). On p. 1, lines 26-30, it is explicitly mentioned that cysteine itself has free-radicals reducing activity; p. 5, line 33 - p. 6, line 20 mentions the synergistic effect of both compounds, which implies that they each have the claimed activity.

It was therefore obvious for the person skilled in the art, knowing from D12 that renal patients undergoing hemodialysis are susceptible to oxidative stress, which can be treated with an intravenous cysteine source, namely N-acetylcysteine, and from D13 that cysteine or cystine can be used interchangeably with N-acetylcysteine for the treatment of conditions caused by oxidative stress, also when administered orally, to at least try to use oral cystine or cysteine for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure, with a reasonable expectation of success.

Therefore, the subject-matter of present claims 1-5 and 7 is obvious in the light of D12 and D13.

(d) As far as the coadministration with other substances, such as taurine, lipoic acid and vitamins A, C and E is concerned, the subject-matter of claim 5 - as far as novel - does not involve an inventive step because each of these compounds individually is known to be useful in the treatment of renal diseases.

Document D14 discloses an antioxidant compositions for companion animals containing vitamin E and/or vitamin C and/or taurine and/or lycopene for the treatment of diseases in which oxidative stress is involved, such as renal disease or renal failure (p. 1, lines 15-21; p. 3, lines 11-15; p. 6, lines 1-2; p. 6, lines 28-30; p. 7, lines 16-19; p. 8, line 24 - p. 9, line 11;

P. 10, line 24 - p. 11, line 14; p. 13, lines 6-14; claims 7-11, 14, 15, 27, 32).

Document D15 teaches the use of alpha-lipoic acid in oral dosage form for the treatment of nephropathy (par. [0001], [0011], [0026]-[0027], [0031]; claim 1).

In the absence of the demonstration of a surprising and/or unexpected effect for each of the claimed combinations, the subject-matter of present claim 5 is considered as obvious, as the skilled person would have expected at least some beneficial effect from the combination of these compounds, in the absence of indications to interactions or other non-beneficial effects obtained by the combination in question.

Re Item VIII

Certain observations on the international application

The use of the expression "such as" in claim 5 has no limiting effect on the scope of the claim, according to the Guidelines C.III.4.6; i.e. the feature following is entirely optional, thus rendering the scope of protection obscure.


PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 889 PCT		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2004/014359		International filing date (day/month/year) 16.12.2004		Priority date (day/month/year) 19.12.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K31/198 A61K31/225 A61K31/185 A61K31/385 A61K31/07 A61K31/375 A61K31/355 A61P13/12 A61P39/06				
Applicant BIO 3 RESEARCH SRL				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 13 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 2 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input checked="" type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 14.10.2005		Date of completion of this report 05.04.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer Cielen, E Telephone No. +31 70 340-4540		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/014359

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-5 as originally filed

Claims, Numbers

1-8 received on 14.10.2005 with letter of 14.10.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 9
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/014359

Box No. II Priority

1. ☒ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☒ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
 - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/014359

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-8

because:

☒ the said international application, or the said claims Nos. 6-8, with respect to industrial applicability, relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*).

☐ no international search report has been established for the said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/014359

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1-8
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-8
Industrial applicability (IA)	Yes: Claims	1-5
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

10/583334

AP3 Rec'd PCT/PTO 16 JUN 2005

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/014359

Re Item I

Basis of the report

The amendments filed with the letter dated 14.10.2005 are in accordance with Article 34(2)(b) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.i. Claims 6-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. Present claims 6-8 involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/EP2004/014359

- D1: US-A-4 794 124 (YAMAMOTO ET AL) 27 December 1988 (1988-12-27)
D2: US-A-4 849 452 (DULCE ET AL) 18 July 1989 (1989-07-18)
D3: WO 93/14750 A (THE ROCKEFELLER UNIVERSITY; ALTEON INC) 5 August 1993 (1993-08-05)
D4: US-A-5 607 974 (DROEGE ET AL) 4 March 1997 (1997-03-04)
D5: US-A-4 792 549 (TAKAHASHI ET AL) 20 December 1988 (1988-12-20)
D6: WO 02/34303 A (NITROMED, INC; TRUSTEES OF BOSTON UNIVERSITY; LOSCALZO, JOSEPH; VITA,) 2 May 2002 (2002-05-02)
D7: US 2002/137785 A1 (KINDNESS GEORGE ET AL) 26 September 2002 (2002-09-26)
D8: US-A-6 060 446 (ZALOGA ET AL) 9 May 2000 (2000-05-09)
D9: DATABASE WPI 6 September 1991 (1991-09-06), Derwent Publications Ltd., London, GB; Class 914, page 2, AN 1991-306713 XP002326744 FUNATO TOSHIAKI ET AL.: "Oral amino acid preparation for cardiac failure" & JP 03 204814 A (OTSUKA SEIYAKU KOGYO KK) 6 September 1991 (1991-09-06)
D10: DE 34 14 491 A1 (DIETL, HANS, DR) 24 October 1985 (1985-10-24)
D11: MOBERLY JAMES B ET AL: "Elevation of whole-body glutathione in peritoneal dialysis patients by L-2-Oxothiazolidine-4-carboxylate, a cysteine prodrug (Procysteine)" JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, vol. 9, no. 6, June 1998 (1998-06), pages 1093-1099, XP008046078 ISSN: 1046-6673
D12: US-B1-6 627 659 (SANTANGELO FRANCESCO) 30 September 2003 (2003-09-30)
D13: WO 00/53176 A (UNI-CI S.R.L; DALL'AGLIO, ROBERTO; BORGONOVO, MARGHERITA; INTROINI, CA) 14 September 2000 (2000-09-14)
D16: M. H. BEERS; R. BERKOW: "The Merck Manual of Diagnosis and Therapy, Seventeenth Edition" 1999, MERCK RESEARCH LABORATORIES, WHITEHOUSE STATION N.J., XP002326823

The following document was cited by the Applicant:

- D17: SANTANGELA F: "Intracellular thiol concentration modulating inflammatory response: Influence on the regulation of cell functions through cysteine

prodrug approach" CURRENT MEDICAL CHEMISTRY, vol. 10, 2003,
pages 2599-2610.

V.iii. Article 33(2) PCT.

(a) The scope of claim 5 for which protection is sought as it is worded is regarded as a so-called "first medical use". Claims drafted in this way are only allowable if no other medical use has been earlier disclosed. Consequently, any document disclosing a medical use of a composition suitable for oral administration comprising cysteine or cystine will be novelty-destroying for the subject-matter of claim 5.

(b) Claims 1-6 relate to the mechanism underlying the treatment of the claimed diseases with cystine and/or cysteine. However, the mere explanation of an effect obtained when using a compound in a known composition, even if the effect was not known to be due to this compound in the known composition, cannot confer novelty on a known process if the skilled person was already aware of the occurrence of the desired effect. Even if the effect on oxidative stress by cystine and/or cysteine is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application, nor can it render the known treatment of a specified pathological condition, in the present case the known haemodialysis treatment of patients suffering from chronic kidney failure with cystine and/or cysteine, novel (see **V.iii(c)10** below). Although the discovery of such a mechanism may be an important piece of scientific knowledge, it cannot be considered as a technical contribution to the art, since it still needs to be turned into a practical application in the form of a specified actual treatment of the pathological condition.

Consequently, whatever the merit of the scientific teaching provided by the application regarding the mechanism of action of the claimed compounds, it is only the therapeutic effect of the medicament, i.e. the use of cystine and/or cysteine in haemodialysis treatment of patients suffering from chronic kidney failure, which is relevant for the assessment of novelty and inventive step.

(c) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 is not new in the sense of Article 33(2) PCT:

1. Document D1 discloses the use of orally administered cysteine for the treatment of diabetic complications, such as nephropathy, which falls within the definition "acute or chronic

kidney diseases" (column 2, lines 25-54; column 6, lines 10-16). The daily dose ranges from 10-5000 mg, in single or divided dosages (column 3, lines 1-13). According to D16, diabetic nephropathy is a major cause of chronic renal failure and the most common cause of end-stage renal disease (Table 222-3; p. 1845, paragraph bridging left- and right-hand column); therefore, treatment of diabetic nephropathy *prevents* chronic kidney failure and end-stage renal disease.

It is recognised that the treatment of diabetic nephropathy by oral cysteine in D1 is not supported by data; however, the present application also provides a *mere statement* about the clinical efficacy of cysteine and/or cystine in the claimed diseases, without any pharmacological data. Therefore, the present description provides *no further evidence* showing the actual claimed effect of cysteine and/or cystine than did the prior art document D1. Accordingly, in the absence, in the patent application as originally filed, of any data providing additional technical information in relation to the actual treatment of the claimed kidney diseases by cysteine and/or cystine compared with the disclosure in the prior art document D1, it must be concluded that the subject-matter of the patent application is anticipated by the disclosure in D1. Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1, 3, 5 and 7-8 is not novel over D1.

2. Document D2 reports the use of L-cysteine in an amount of 0.75g/dose for the treatment of nephro-urological disorders, such as kidney stones, a disease which falls within the definition "acute or chronic kidney diseases" (column 2, lines 24-44; column 2, line 60 - column 3, line 11; claims). Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1, 3, and 5 is not novel over D2.

3. Document D3 teaches the use of an agent which inhibits the formation of advanced glycosylation end products of target proteins, such as cysteine, for the treatment of diabetic kidney disease or glomerulonephritis, which fall within the definition "acute or chronic kidney diseases" (p. 5, line 13 - p. 6, line 6; p. 6, lines 29-32; p. 7, lines 14-20; p. 17, lines 6-22); claims 1, 7, 15, 17, 18, 31). The compositions can be administered orally (claim 14). According to D16, glomerulonephritis is a major cause of acute renal failure (Table 222-1); therefore, treatment of glomerulonephritis *prevents* acute kidney failure.

Again, the fact that D3 contains no data supporting the actual treatment of diabetic kidney disease or glomerulonephritis by oral cysteine cannot render the present claims novel over D3, as data are also lacking in the present application (see also item **V.iii(c)(1)**). Moreover, each feature (cysteine, oral administration, diabetic kidney disease) is claimed separately as a preferred embodiment. Therefore, and in view of item **V.iii(a)**, the subject-

matter of present claims 1 and 5 is not novel over D3.

4. The subject-matter of the present application can be regarded as a selection invention over D4, which therefore does not prejudice novelty.

5. Document D5 discloses the use of an amino acid composition, containing cysteine or cystine as preferred amino acids, in combination with other amino acids, for the treatment of patients with renal diseases, which fall within the definition "acute or chronic kidney diseases" (column 1, lines 5-9; column 2, lines 58-67; examples 1, 2, 4-6; claims). D5 relates to a *combination* of active agents including cysteine or cystine; from column 1, lines 62-64, it is clear that cysteine actively contributes to the treatment (i.e. it is not an excipient). It is to be noted that present claims 1-8 *do not exclude* the presence of other active agents.

What exactly the mechanism is underlying the treatment of renal diseases with cysteine in combination with the other active agents, is not relevant for the assessment of novelty, since the compound used and the disease treated are the same in D5 and in the present application (see also item **V.iii(b)**).

Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1 and 5 is not novel over D5.

6. The subject-matter of the present application can be regarded as a selection invention over D6, which therefore does not prejudice novelty.

7. Document D7 discloses a combination of a leukotriene antagonist and cystine or cysteine to combat inflammatory diseases, such as ischemic renal failure, which falls within the definition "acute or chronic kidney diseases" (par. [0002], [0004], [0009], [0015], [0018], [0042], [0044]-[0045]; claims 1, 29). The administration can be oral, e.g. 140 mg twice a day (par. [0034]). Since cyst(e)ine is a preferred embodiment (see e.g. claim 1), the choice of ischemic renal failure out of a list of diseases cannot be considered as a selection invention.

As in item **V.iii(c)(5)**, the fact that D7 relates to a *combination* of active agents including cysteine or cystine does not render the present claims novel over D5, as they do not exclude the presence of other active agents. Equally, the exact function of cyst(e)ine in the combination with a leukotriene antagonist, is of no relevance for the assessment of novelty, since the compound used and the disease treated are the same in D7 and in the present application (see also item **V.iii(b)**).

Therefore, and in view of item **V.iii(a)**, the subject-matter of present claims 1 and 5 is not novel over D7.

8. In document D8, the use of a nutritional composition to prevent or treat acute renal failure, which falls within the definition "acute or chronic kidney diseases", is disclosed

(column 1, line 60 - column 2, line 2; column 2, lines 27-30; column 5, line 30 - column 6, line 59; claims 1, 2, 6). Cysteine may be used to prevent injury to the kidney (column 4, lines 31-40). It is to be noted that the dosage of cystine and/or cysteine disclosed in claims 6-8 does not give any indication about the time-frame used; any dosage disclosed in the prior art is therefore novelty-destroying for this feature. Therefore, and in view of items **V.iii(a)** and **V.iii(c)(5)** (combination), the subject-matter of present claims 1, 5 and 7 is not novel over D8.

9. Document D9 discloses an oral amino acid preparation for renal insufficiency, which falls within the definition "acute or chronic kidney diseases", containing cysteine or cystine. Therefore, and in view of items **V.iii(a)** and **V.iii(c)(5)** (combination), the subject-matter of present claims 1 and 5 is not novel over D9.

10. Document D10 discloses oral amino acid mixtures, which may contain cysteine or cystine, for the treatment of acute renal insufficiency or chronic renal insufficiency, with or without dialysis (claims 1, 3, 5, 6; p. 3, lines 1-32; p. 4, line 11 - p. 5, line 25; p. 6, lines 26-30). The composition improves the therapy outcome for patients on dialysis or allows to postpone a dialysis treatment; this implies that it is administered before dialysis (p. 3, lines 9-10). ➤

According to D16, untreated chronic renal failure progresses from moderate to end-stage renal disease (p. 1847, left-hand column, par. 4); therefore, treatment or prevention of chronic renal failure prevents end-stage renal disease.

Therefore, and in view of items **V.iii(a)**, **V.iii(b)**, **V.iii(c)(5)** (combination) and **V.iii(c)(8)** (dosage), the subject-matter of present claims 1, 2, 4 and 5-8 is not novel over D10. ¶

11. Document D11 reports the use of oral L-2-Oxothiazolidine-4-carboxylate (OTZ), a cysteine prodrug, in peritoneal dialysis, a procedure different from the presently claimed haemodialysis. Therefore, D11 is not prejudicial to the novelty of the present claims.

V.iv. Article 33(3) PCT.

(a) The problem to be solved by the present application is the provision of alternative medicaments for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure or for the treatment or prevention of acute or chronic kidney diseases or end-stage renal disease. The proposed solution is the use of oral cystine and/or cysteine.

(b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 does not involve an inventive step in the sense of Article 33(3)

PCT, as it is also not novel.

(c) As far as the prevention and treatment of acute or chronic kidney diseases, including acute or chronic kidney failure, or the *prevention* of End-stage Renal Disease is concerned (claims 1 (and dependent thereon claim 3) and 7-8), even if novelty could be restored, the present application would very likely lack inventive step over each of D1-D3, D5, D7-D10, which clearly teach the use of oral cysteine or cystine for the claimed diseases.

(c) As far as the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure is concerned (claims 1 (and dependent claim 3), 2, 4 and 6), the following is to be noted: Provided the novelty objection (see item V.iii(c)(10)) could be overcome, the subject-matter of these claims may involve an inventive step for the following reasons:

Document D12, which can be considered to represent the closest state of the art, discloses that intravenous administration of N-acetylcysteine decreases the effects of oxidative stress in patients with renal disease undergoing haemodialysis. A study is mentioned wherein the oral administration of N-acetylcysteine for the same purpose was ineffective.

The subject-matter of present claims 1-4 and 6 differs herefrom in that oral cysteine or cystine is used for the same therapeutic purpose.

The problem to be solved by the present application may therefore be regarded as the provision of an alternative cysteine source, offering advantages in terms of cost, ease and safety, for the prevention and/or treatment of oxidative stress resulting from haemodialysis treatment in patients with chronic kidney failure (present description, p. 5, lines 4-8).

The solution proposed in claims 1-4 and 6 of the present application may be considered as involving an inventive step for the following reasons:

From document D13, it is known that cysteine has free-radical reducing activity (p. 1, lines 26-30) and that cysteine, cystine or N-acetylcysteine can be used (in a synergistic combination with lipoic (thioctic) acid) for the treatment of conditions caused by oxidative stress (p. 1, lines 3-15; p. 1, line 26 - p. 2, line 1; p. 2, lines 22-34; claims 1, 3, 4, 7).

However, the skilled person would not be incited to replace intravenous N-acetyl cysteine used in D12 by oral cyst(e)ine, for the following reasons:

(i) cysteine is reported to be less stable, more toxic and less soluble than its prodrug N-acetyl cysteine (see D17; p. 2605, left-hand column, par. 1-2, 7), and

(ii) D12 discloses that *oral* N-acetylcysteine is ineffective to decrease the effects of oxidative stress in patients with renal disease undergoing haemodialysis.

Re Item VIII

Certain observations on the international application

Present claims 1, 3 and 5 refer to the treatment of diseases which actually are not well defined. The use of the definitions "acute and chronic kidney diseases" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT.

It is not fully possible to determine the diseases for which protection might legitimately be sought. The only diseases which appear to be clear are the real and defined diseases mentioned in claims 2, 4 and 6-8.